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only

50. (New) The method of claim 1, wherein at least one of said characteristics is determined by electrophoresis.

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REMARKS

Claims 1-43 are pending, and claims 1-23 are under examination. Claims 1 and 13 have been amended. New claims 44-49 have been added. Support for the amendment and new claims can be found throughout the specification and the claims as filed. Claims 1 and 13 have been amended to incorporate the definition of annotated polypeptide index. Support for the amendment to claims 1 and 13 can be found, for example, on page 18, line 29, to page 19, line 2. Support for new claims 44-49 can be found, for example, on page 54, line 18, to page 55, line 5. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth the amendment to the claims in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

Applicants appreciate Examiner Tran's time and helpful discussion in the telephone conference with one of the inventors, Dr. David Goodlett, and Applicants' representative on January 9, 2003.

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Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 13-23 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. As discussed in the telephone interview with Examiner Tran, Applicants believe that claim 13 and its dependent claims are clear and definite. Nevertheless, the preamble of claim 13 has been amended to recite a method of identifying "and quantitating" a polypeptide to refer to the quantitating of step (d). Applicants submit that claim 13 and its dependent claims are clear and definite and respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

The rejection of claims 1, 2 and 8-12 under 35 U.S.C. § 102(b) as allegedly anticipated by Yates, J. Mass Spectrom. 33:1-19 (1998), or Link et al., Nat. Biotechnol. 17:676-682 (1999), is respectfully traversed. As discussed in the telephone interview with Examiner Tran, neither of Yates nor Link et al. teach the use of an annotated polypeptide index, where the annotated polypeptide index comprises a least one empirically determined characteristic for each of the polypeptides in the index. Claim 1 has been amended to incorporate the definition of an annotated polypeptide index and explicitly recite that the index comprises at least one empirically determined characteristic for each of the polypeptides in the index.

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As discussed in the telephone interview with Examiner Tran, neither of Yates or Link et al. teaches the use of an annotated polypeptide index. In both references, peptides determined using mass spectrometry are compared to a sequence database of predicted values but not to an index comprising at least one empirically determined characteristic for each of the polypeptides in the index.

Regarding Yates, this reference describes the use of predicted values from database sequences. In particular, Yates indicates on page 7, column 2, last paragraph, that the "observed  $m/z$  values are compared with the values predicted after digestion of each protein in the database with a site specific enzyme" (emphasis added). Similarly, Link et al. describe on page 676, column 2, first complete paragraph, the use of the SEQUEST algorithm and that "acquired fragmentation spectra of peptides are correlated with predicted amino acid sequences in translated genomic databases" (emphasis added). These references are clearly describing the use of databases based on predicted values, not the annotated polypeptide index comprising at least one empirically determined characteristic, as in the claimed methods. Applicants therefore respectfully maintain that neither Yates nor Link et al. can anticipate the claimed methods.

With regard to the definition of "empirical" provided by the Examiner in the Office Action, Applicants submit that the dictionary definition of "empirical" is consistent with the use of this term in the specification. As indicated in the dictionary definition provided in the Office Action, "empirical"

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is defined as: (1a) "Relying upon or gained from experiment or observation;" (1b) "Capable of proof or verification by means of experiment or observation;" (2) "Relying solely on practical experience and without regard for theory or system." Each of these definitions is consistent with empirical referring to experimentally determined or observed characteristics, as described in the specification (page 18, line 24, to page 19, line 5; page 31, line 14, to page 32, line 9; and in the Examples, pages 66-78). Applicants therefore respectfully disagree with the assertion on page 6, paragraph 11, of the Office Action that there is no distinction between empirically determined characteristics and predicted values. Moreover, in light of the clear meaning of an empirically determined characteristic, as taught in the specification and as understood by those skilled in the art, it is respectfully submitted that the claimed method using an annotated polypeptide index is distinct from the predicted databases used in Yates or Link et al. Accordingly, neither of Yates or Link et al. can anticipate the claims, and Applicants respectfully request that this rejection be withdrawn.

#### Rejections Under 35 U.S.C. § 103

The rejection of claims 3, 13, 14 and 20-23 under 35 U.S.C. § 103 as allegedly obvious over Yates, *supra*, or Link et al., *supra*, in view of Mann, Nat. Biotechnol. 17:954-955 (1999), or Gygi et al., Nat. Biotechnol. 17:994-999 (1999), is respectfully traversed. Applicants maintain that these claims

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are unobvious over Yates or Link et al., alone or in combination with Mann or Gygi et al.

As discussed above, neither of Yates or Link et al. teaches the claimed methods using an annotated polypeptide index where at least one of the characteristics of each of the polypeptides in the index is determined empirically. Furthermore, neither Mann or Gygi et al. cures the deficiencies of either Yates or Link et al. The combination of Yates or Link et al. with either of Mann or Gygi et al. does not teach or suggest the claimed methods using an annotated polypeptide index but, at best, describes the use of databases of predicted values only. Absent such a teaching or suggestion, neither Yates or Link et al., alone or in combination with Mann or Gygi et al., can render the claimed invention obvious. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 4-8 and 15-19 under 35 U.S.C. § 103 as allegedly obvious over Yates, *supra*, or Link et al., *supra*, in view of Masselon et al., Anal. Chem. 72:1918-1924 (2000), is respectfully traversed. Applicants maintain that these claims are unobvious over Yates or Link et al., alone or in combination with Masselon et al.

As discussed above, neither of Yates or Link et al. teaches the claimed methods using an annotated polypeptide index where at least one of the characteristics of each of the polypeptides in the index is determined empirically. Furthermore, Masselon et al. does not cure the deficiencies of

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either Yates or Link et al. The combination of Yates or Link et al. with Masselon et al. does not teach or suggest the claimed methods using an annotated polypeptide index but, at best, describes the use of databases of predicted values only. Absent such a teaching or suggestion, neither Yates or Link et al., alone or in combination with Masselon et al., can render the claimed invention obvious.

Applicants respectfully disagree with the assertion on page 7, paragraph 13, of the Office Action that Applicants do not claim increased ppm values directed to decreasing mass accuracy. As discussed with the Examiner in the telephone conference, higher ppm values refer to decreased mass accuracy (page 24, lines 5-7). Furthermore, Masselon et al. describes the use of high mass accuracy measurements (page 1918, second column, first complete paragraph), not the decreasing mass accuracy recited in claims 4-8 and 15-19, respectively. Moreover, the use of decreasing mass accuracy is not the mere optimization of a range, as asserted in the Office Action, but rather reflects that the method can be used with lower mass accuracy instruments and still achieve the desired identification of a polypeptide (see specification, page 23, line 28, to page 24, line 24).

Applicants maintain, for the reasons of record and as discussed above, that the claimed methods are unobvious over Yates or Link et al., alone or in combination with Masselon et al. Accordingly, Applicants respectfully request that this rejection be withdrawn.


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**CONCLUSION**

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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**APPENDIX A**

1. (Twice amended) A method for identifying a polypeptide, comprising:

(a) determining two or more characteristics associated with said polypeptide, or a peptide fragment thereof, one of said characteristics being mass of a peptide fragment of said polypeptide determined by mass spectrometry;

(b) comparing said characteristics associated with said polypeptide to an annotated polypeptide index, said annotated polypeptide index comprising at least one empirically determined characteristic for each of the polypeptides in the index; and

(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics.

13. (Twice amended) A method for identifying and quantitating a polypeptide, comprising:

(a) determining two or more characteristics associated with said polypeptide, or a peptide fragment thereof, one of said characteristics being mass of a peptide fragment of said polypeptide determined by mass spectrometry;



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(b) comparing said characteristics associated with said polypeptide to an annotated polypeptide index, said annotated polypeptide index comprising at least one empirically determined characteristic for each of the polypeptides in the index;

(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics; and

(d) quantitating the amount of said identified polypeptide in a sample containing said polypeptide.